The Normal and Diseased Pericardium: Current Concepts of Pericardial Physiology, Diagnosis and Treatment

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The past quarter century has seen remarkable contributions to understanding the role of the pericardium in health and disease and to diagnostic methods in the context of significant changes in the clinical spectrum of acute pericarditis, pericardial effusion and their sequelae. *Anatomic studies* have demonstrated pericardial ultrastructure and its relation to function and delineated the pericardial lymphatics and their participation in inflammation and tamponade. *Physiologic investigations* have revealed the pericardium's mechanical, membranous and ligamentous functions and its role in ventricular interaction, pericardial modification of cardiac responses during acute cardiocirculatory loading and effects on diastolic function (and, at high filling pressures, systolic function), including reduction by pericardial fluid of true filling pressure—the myocardial transmural pressure. The diastolic mean pressure plateau and phasic venoatrial pressure and flow during cardiac tamponade have been further characterized and the mechanisms producing pulsus paradoxus have been elucidated, including the importance of inspiratory increase in right ventricular filling. A far reaching compensatory response to tamponade has been revealed, particularly adrenergic stimulation, and, over time, blood volume expansion. Right heart tamponade and low pressure tamponade have been identified and the importance of the pericardium in the restrictive dynamics of right ventricular myocardial infarction has been demonstrated. *Constrictive pericarditis*, and the currently more common *effusive-constrictive pericarditis*, have been studied, in depth, clinically and hemodynamically.

***Cardiography in pericardial disease* now includes M-mode and two-dimensional echographic studies, enabling rapid diagnosis and further physiologic study in cardiac tamponade and constriction. The four stages of typical *electrocardiographic evolution* in acute pericarditis and atypical variants have been codified and characteristic PR segment deviations identified. The nonetiologic role of acute pericarditis in *arrhythmias* has been clarified in prospective clinical and postmortem investigations. Electric alternation has been elucidated and its relation to cardiac "swinging" has been at least partly explained. Special roles now exist for *contrast roentgenography, computed tomography* (especially for cysts) and *radionuclide imaging. Clinical advances* in pericardial disease include changes in the prevalence of established etiologies and identification of new etiologies, for example, immunopathic processes to explain recurrent pericarditis and the post-injury (including postoperative) pericardial syndromes. New forms of constriction—uremic, postoperative, radiation—have appeared in increasing numbers. The *pericardial rub* has been characterized and codified, confirming a typical three-component structure (with frequent exceptions).**

The pericardium has fascinated physicians since antiquity (1), largely because pericardial syndromes produce a range of often spectacular clinical and physiologic abnormalities and because the pericardium is susceptible to involvement by every kind of disease. The last quarter century has seen five major books on the pericardium and its disorders (2–6) and brilliant advances in elucidating pericardial dynamics, particularly by cardiology groups led by Shabetai and Fowler (7–19), Guntheroth (20,21), Reddy (22), Friedman (23–25) and a host of physiologists (26–38). Clinical and laboratory investigations have clarified the hemodynamics and the noninvasive registration of pericardial diseases and have delineated the functions of the normal pericardium in facilitating cardiac action and chamber interactions. Disease may compromise pericardial functions and convert the pericardium from the heart's protector to its deadly enemy.

Because of space limitations I have necessarily condensed this review of salient contributions of the past 25 years into a synthesis of state-of-the-science and state-of-the-art concepts and have largely excluded discussion of experimental and clinical methodology. Recent work sup-

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ports some and refutes other earlier studies; important references more than 25 years old are found in reference 6.

Pericardial Anatomy

Ultrastructure

Gross pericardial anatomy, including mesothelial, fibrous, elastic, vascular and lymphatic elements, is well understood; even "subgross" analysis, the dynamic orientation of fibers in the parietal pericardium, has been characterized (6). Ferrans et al. (39) and Roberts and Spray (40) recently reported ultrastructural details, including serosal cell *microvilli*, that presumably bear friction and facilitate fluid and ion exchange. Although oblique during diastole, these become more perpendicular during systole. Despite a basal lamina, pericardial mesothelial cells detach easily. Yet, during systole, the visceral pericardial serosa becomes corrugated and the cells bulge and thicken. Indeed, the mesothelial cell monolayer has considerable overlap and marked interdigitations between adjacent cells, a design that would permit changes in the surface configuration but maintain mechanical stability. Among the many cell constituents are *actin filaments*, involved in active change in cell shape, and *cytoskeletal filaments*, providing structural support.

Significance of Pericardial Lymphatics

Miller et al. (41) extensively studied the cardiopericardial lymphatics. Myocardial lymph drains to the subepicardium and ultimately to the mediastinum and right heart cavities. In heart failure, *hydropericardium* results from interference by elevated central venous pressure with myocardial venous and lymph drainage. Inflammations damage the visceral pericardium, also interfering with epicardial venous and lymph flow, with loss of interstitial fluid from the myocardium to the pericardial space. Because most pericarditis with effusion probably is myopericarditis, all *inflammatory effusions* may exude through the epicardial surface.

Pericardial Physiology: A Synthesis of Laboratory and Clinical Observations

Table 1 presents a concept derived from experimental and clinical observations (2–38,42)—a synopsis of the complicated roles of the pericardium and its components. These roles are divided into mechanical, membranous and ligamentous functions (4). *Mechanical functions* relate to relative stiffness of the parietal pericardium, its effects as a fluid-filled chamber at slightly subatmospheric pressure and incompletely understood circulatory "feedback" regulation by way of pericardial neuroreceptors and mechanoreceptors. *Membranous functions* result from the physical presence of

Table 1. Physiology of the Normal Pericardium

Mechanical Function: Promotion of Cardiac Efficiency, Especially During Hemodynamic Overloads

I. Relatively inelastic cardiac envelope
   - A. Limitation of excessive acute dilation
   - B. Protection against excessive ventriculoatrial regurgitation
   - C. Maintenance of normal ventricular compliance (volume-elasticity relation)
   - D. Defense of the integrity of the Starling curve: Starling mechanism operates uniformly at all intraventricular pressures because presence of pericardium:
     1. Maintains ventricular function curves
     2. Limits effect of increased left ventricular end-diastolic pressure
     3. Supports output responses to
        a) venous inflow loads and atrioventricular valve regurgitation (especially acute)
        b) rate fluctuations
     4. Hydrostatic system (pericardium plus pericardial fluid) distributes hydrostatic forces over epicardial surfaces
        a) Favors equality of *transmural* end-diastolic pressure throughout ventricle, therefore uniform stretch of muscle fibers (preload)
        b) Constantly compensates for changes in gravitational and inertial forces, distributing them evenly around the heart
   - E. Ventricular interaction: relative pericardial stiffness
     1. Reduces ventricular compliance with increased pressure in the opposite ventricle (e.g., limits right ventricular stroke work during increased impedance to left ventricular outflow)
     2. Provides mutually restrictive chamber favoring balanced output from right and left ventricles integrated over several cardiac cycles
     3. Permits either ventricle to generate greater isovolumic pressure from any volume
   - F. Maintenance of functionally optimal cardiac shape

II. Provision of closed chamber with slightly subatmospheric pressure in which:
   - A. The level of *transmural* cardiac pressures will be low, relative to even large increases in "filling pressures" referred to atmospheric pressures
   - B. Pressure changes aid atrial filling via more negative pericardial pressure during ventricular ejection

III. "Feedback" cardiocirculatory regulation via pericardial servomechanisms
   - A. Neuroreceptors (via vagus): lower heart rate and blood pressure
   - B. Mechanoreceptors: lower blood pressure and contract spleen

IV. ?? Limitation of hypertrophy associated with chronic exercise

Membranous Function: Shielding the Heart

I. Reduction of external friction due to heart movements

II. Barrier to inflammation from contiguous structures

III. Buttressing of thinner portions of the myocardium
   - A. Atria
   - B. Right ventricle

IV. Defensive immunologic constituents in pericardial fluid

V. Fibrinolytic activity in mesothelial lining

Ligamentous Function: Limitation of Undue Cardiac Displacement

the pericardium. *Ligamentous function* limits cardiac displacement. Mechanical functions and the behavior of intrapericardial pressure largely explain both helpful and harmful pericardial influences during circulatory overload, and the dynamics of tamponade, constriction and pulsus paradoxus.

Although *removal of the pericardium* has little effect on ventricular function, at any cardiac volume pericardiectomy decreases diastolic and developed pressures. Indeed, ventricles without a pericardium have less steep diastolic pressure-volume curves, as seen with volume loading and increasing filling pressures. At elevated diastolic pressures—especially when unilateral, as in acute volume overload—the pericardium becomes restrictive; chronic overloading abolishes the restriction as a result of pericardial enlargement and ventricular hypertrophy (38). Although the pericardium primarily affects diastolic function, it should secondarily affect systolic performance, even though it may do so only at very high filling pressures (42).

Pericardial pressure curves resemble a mirror image of the pressure in the adjacent cardiac chamber. At normal cavitary pressures, *pericardial transmural* pressure is 0, because pericardial pressure is approximately equal to, and varies with, pleural pressure at the same hydrostatic level. Pericardial pressure affects *myocardial* transmural pressure by the relation: transmural pressure = cavitary pressure minus adjacent intrapericardial pressure. Because myocardial transmural pressure is the actual chamber distending (that is, filling) pressure, the normally negative pericardial pressure produces a distending pressure that is higher than cavitary pressure; thus, left ventricular transmural pressure = left ventricular pressure minus (*negative*) pericardial pressure = left ventricular pressure plus pericardial pressure.

Normal respiratory effects. Because the pericardium transmits important respiratory effects, inspiratory reduction of pleural pressure reduces pericardial, right atrial, right ventricular, pulmonary wedge and systemic arterial pressures by a few millimeters of mercury. Because pericardial pressure decreases more than atrial pressure, right atrial and other central transmural pressures increase, augmenting right heart filling. Inspiration thus increases right ventricular preload, an effect that varies inversely with pleural pressure and directly with systemic venous pressure. Although pulmonary artery flow velocity increases with inspiration, both transmural pressure and flow decrease in the aorta and peripheral arteries at a time when systemic venous return is increasing. Moreover, augmented inspiratory right ventricular output "pools" temporarily in the lungs, and left heart filling is reduced. Although left ventricular transmural pressure increases with inspiration, this slightly increases left ventricular "afterload," contributing to reduced left ventricular output. Thus, respiratory changes in arterial blood pressure vary directly with changes in pleural pressure.

Pressure breathing. Positive end-expiratory pressure and intermittent positive pressure breathing increase pulmonary artery transmural pressure, resulting in increased right ventricular size. The pericardium imposes ventricular interaction and septal bulging so that left ventricular chamber compliance and size decrease, shifting the left ventricular pressure-volume relation to a stiffer curve (2). Positive end-expiratory pressure and intermittent positive pressure breathing thus tend to decrease cardiac output and have long been contraindicated in cardiac tamponade and other low output states (6).

Cardiac Tamponade

Mechanisms (Fig. 1). Cardiac tamponade is defined as hemodynamically significant cardiac compression by accumulating pericardial contents that evokes and defeats compensatory mechanisms. Experimental and clinical investigations (2,3,43) have clarified the mechanisms of tamponade and compensatory responses. The key effect of relentlessly increasing intrapericardial pressure is progressive *reduction of ventricular volume*, producing rapidly rising diastolic pressures that resist ventricular filling to the point where even a good ejection fraction cannot avert a critically reduced stroke volume at any heart rate. The change from negative to positive pericardial pressure, with both ventricles filling against a common (pericardium plus fluid) stiffness, evokes corresponding increases in left and right atrial pressures. Because transmural pressure—cavitary pressure *minus* (now *positive*) pericardial pressure—is thereby reduced, the distending (filling) pressure progressively decreases.

Although the right ventricle is compressed during tamponade (44), and its outflow tract collapses in early diastole (45,46), it expands during inspiration. Pericardial pressure quickly exceeds early diastolic atrial pressure (16), impeding atrial emptying and the corresponding reduction in pressure—visible as amputation of the atrial *y* descent. Absence of the *y* descent with a prominent *x* descent is characteristic of pure tamponade and implies that the atria fill only during ventricular ejection consistent with slightly decreased compression due to systolic reduction in cardiac volume. The course of ventricular filling is incompletely understood, but it is delayed and the ventricles may fill only during atrial systole (45)—a likely event at least at rapid heart rates. *Extreme tamponade* causes pericardial pressure to exceed cavitary pressure throughout diastole (47). This produces persistently negative myocardial transmural pressure, suggesting filling by diastolic suction (5).

Compensatory responses (Fig. 1). In response to increased systemic venous pressure, *increased blood volume* supports cardiac filling (but only with sufficient time—this increase is not seen in rapid intrapericardial hemorrhage). *Adrenergic stimulation* and *increased atrial pressure* evoke increased systemic and pulmonary *venous pressures* and *tachycardia*, which tend to maintain cardiac output at low

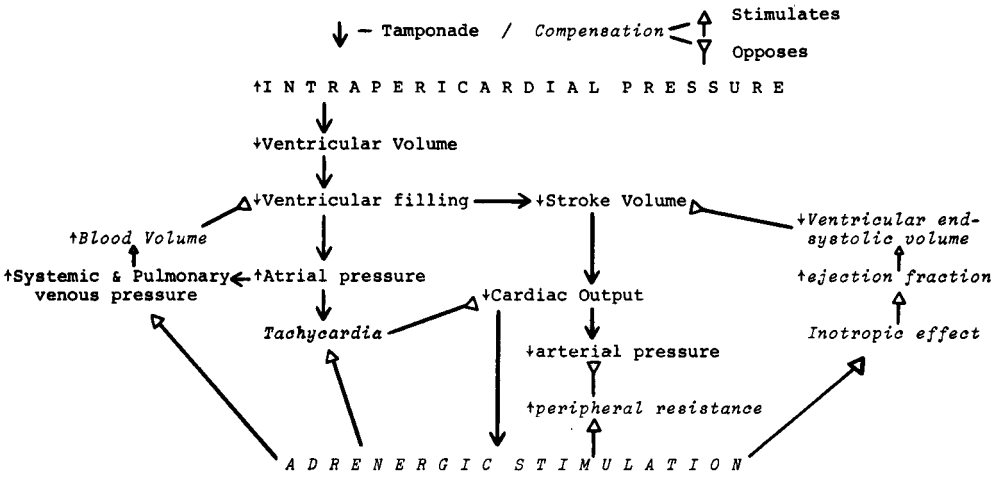

Figure 1. *Physiology of cardiac tamponade including compensatory mechanisms.* Decreased ventricular filling through external compression and reduced transmural pressure (see text) results in reduced stroke volume, cardiac output and arterial pressure and increased atrial and venous pressures. Compensatory responses (**italics**) (**open-headed arrows directed upward**) support the points of attack of tamponade (**open reverse arrowheads**).

stroke volumes (however, heart rates in clinical tamponade are often only modestly increased). Adrenergic stimulation also increases *peripheral resistance* to support decreasing arterial pressure, but a most important consequence is its *inotropic effect*, which improves the ejection fraction as a result of greater systolic emptying and therefore greater stroke output.

Effects of tamponade on coronary flow. Coronary artery flow is reduced by tamponade and may become retrograde during systole (48–50) (although retrograde flow may be normal within intramural arteries). Flow disturbances are not surprising if one considers the diastolic pressure "vise" clamping the myocardium (43,51). It is not clear when significant myocardial ischemia occurs, except in severe experimental tamponade, in which there are selective subendocardial hypoperfusion and hemorrhages (50). In cases of less severe tamponade, the decrease in coronary flow may be proportional to the reduced work of the heart.

Pulsus Paradoxus

Mechanism (Fig. 2). Pulsus paradoxus—exaggeration of the normal inspiratory decrease in systemic blood pressure—has been extensively investigated (13,20–28). Although normal respiratory pressure changes are greater for the right side of the heart, in tamponade pulsus paradoxus involves fluctuations in aortic flow and pressure similar to those in the pulmonary artery—evidence for the increased effect on ventricular interaction of a tight (though yielding) pericardium. Pulsus paradoxus is always the net effect of several mechanisms of individually varying contributions in a given case.

In tamponade, pulsus paradoxus implies a very large reduction in ventricular volume (25). Its mechanism resembles that of normal breathing, except that inspiratory pericardial pressure briefly decreases (but less than pleural pressure), then increases as the right ventricle fills. Absolute cardiac filling is less than normal, but *directional changes in flow and filling related to respiration remain the same.* Thus, inspiration accelerates flow in the venae cavae to increase right heart filling (11,13,14,17). Increased right ventricular volume causes the interventricular septum to bulge to the left and increases pericardial pressure, further decreasing left ventricular transmural pressure. (Left ventricular output can decrease within a beat of beginning inspiration [52], suggesting an additional, poorly understood contribution to pulsus paradoxus.) External compression by pericardial pressure and internal compression by septal shift reduce left ventricular volume so that the left ventricle operates on a steeper Starling curve and resists filling even more during inspiration. (The mitral valve may open during inspiration only with atrial systole.) Thus, left ventricular stroke output decreases, as is reflected in the inspiratory decrease in arterial flow and pressure. The difference between inspiratory and expiratory measurements is augmented by two other factors: 1) the time for the inspiratory increase in right ventricular output to cross the lungs and appear in the left ventricle, which is partly a function of heart rate, and 2) the transmission of inspiratory negative pleural pressure to the aorta and systemic arteries. (To an unknown degree the lungs may act as a capacitor, "pooling" right ventricular output during inspiration and abolishing or reversing the pulmonary artery-left atrial gradient to reduce left atrial filling.) Left ventricular embarrassment is reflected in systolic time intervals by a greater than normal inspiratory increase in left ventricular pre-ejection period and decrease in ejection time index (53).

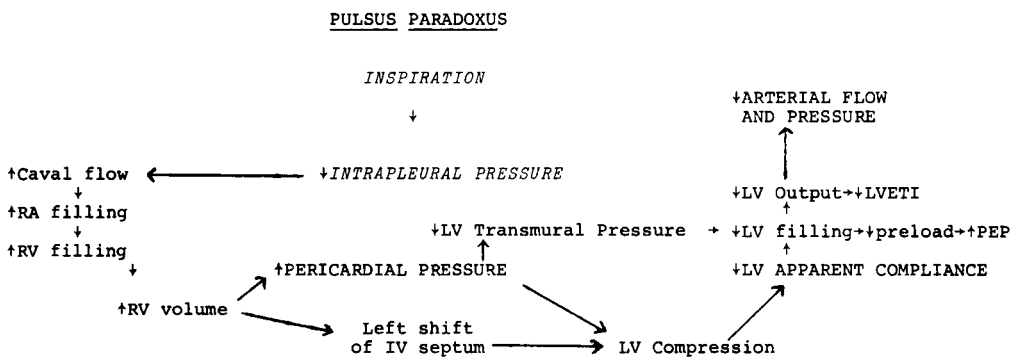

Figure 2. *Pulsus paradoxus.* Inspiration decreases intrapleural pressure with sequential results differing from normal because pericardial pressure increases and left ventricular (LV) transmural pressure decreases after an increase in right ventricular (RV) volume further increases pericardial pressure. *Not shown:* transient initial decrease in pericardial pressure; decrease in pleural pressure decreasing aortic flow and pressure; capacitor function of lungs, pooling right ventricular output to decrease left atrial inflow (see text). IV = interventricular; LVETI = left ventricular ejection time index; PEP = pre-ejection period; RA = right atrium.

Absence of pulsus paradoxus. Pulsus paradoxus may be absent in certain situations. Pulsus paradoxus requires filling of both ventricles against a common pericardial stiffness plus respiratory changes alternately favoring right and left heart filling. Advanced *left ventricular hypertrophy* or *severe left heart failure* may maintain left ventricular filling pressures well above right ventricular and pericardial pressures. In these cases, pericardial pressure matches only right ventricular filling pressure, because both are determined by the compliance of the tense pericardial sac, while left ventricular filling pressure is determined by greatly reduced compliance owing to hypertrophy, dilation or fibrosis. In *atrial septal defect,* the increased systemic venous return is balanced by shunting to the left atrium. *Severe aortic incompetence* produces regurgitant filling great enough to damp respiratory fluctuations. Also, respiratory changes may not be measureable in *severe tamponade* with extreme hypotension.

Right heart tamponade is seen both with a low compliance left ventricle that does not manifest pulsus paradoxus and after cardiac surgery. After surgery, loculated pericardial fluid may cause systemic congestion with appropriate dynamics, but left heart diastolic pressures do not match and systemic pulsus paradoxus does not occur. *Low pressure tamponade* (2,54) occurs in some patients with pericardial fluid, but symptoms are few and there is no hypotension. Right-sided pressures are slightly raised with abnormal pulse contours, because of only slightly increased pericardial pressure equilibrating with right atrial pressure. This occurs as a stage between lax and "tight" pericardial effusions and in effusions complicated by low blood volume. Any further decrease in blood volume can precipitate florid tamponade at lower pericardial pressure than occurs with normal or increased blood volume.

Management of cardiac tamponade. Definitive management is *removal of pericardial fluid* by paracentesis or surgical drainage. Pericardial catheterization has been introduced to permit optimal drainage, minimal trauma and protection against refilling (6,55). Recently, subxiphoid extrapleural surgical drainage (56,57) has effectively relieved tamponade and permitted digital and endoscopic pericardial exploration. Based on the physiology of tamponade (Fig. 1), *medical management* is designed either to attack key points in the tamponade sequence or to bolster the compensation sequence, or both. These methods include: 1) *blood volume expansion* with intravenous fluids; 2) *stroke volume increase* with inotropic agents, either those like dopamine that do not increase systemic resistance or those like norepinephrine that *support systemic resistance* in severe hypotension; 3) the use of *afterload-reducing agents* (58) in patients with adequate blood pressure; and 4) combined therapy (for example, blood volume expansion plus afterload reduction). Despite the effect of vasodilator drugs and volume expansion on experimental tamponade, trials in patients who are not hypovolemic have been disappointing; prompt drainage of effusions is the treatment of choice (59).

Constrictive Pericarditis

Constriction is less common and less experimentally studied than tamponade but its hemodynamics are well known (2–5). The heart is compressed when its volume approximates pericardial volume in diastole. Like tamponade, constriction thus severely limits ventricular filling with equalization of left and right heart filling pressures, but unlike tamponade, the heart is encased in a quasi-unyielding shell that does not transmit fluctuating pleural pressure. Thus, there is minimal respiratory change in cardiac pressures, though jugular venous pressure may increase during inspiration (Kussmaul's sign). Any inspiratory decrease in arterial pressure in *pure* constriction is slight—nearly always less than 10 mm Hg; any more suggests residual tamponading fluid or pulmonary disease.

In constriction, end-diastolic right ventricular pressure is

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at least one-third of its systolic pressure (which is usually 30 mm Hg or more). Unlike tamponade, venous and atrial pressures show prominent *y* and *x* troughs. As in the normal pericardium and in tamponade, the *x* descent occurs during ventricular ejection when the atrioventricular valves move toward the outflow tracts. Diastolic pressure has an early dip usually followed by a plateau of diastasis that is at a common pressure load for both ventricles (''square root sign'') (5). Because the atrioventricular valves are open, the atrial *y* descent is the result of the dip and the accompanying torrential early diastolic ventricular filling that terminates abruptly in association with a loud third heart sound as the ventricles reach their constricted limit (5). (Evidence of ventricle-chest wall contact in producing a third heart sound [60] has been challenged [61]). A few patients with some ''give'' in the constricting tissue have a telediastolic ''atrial kick'' in ventricular pressure and a corresponding fourth heart sound (62). Myocardial inotropic function is preserved (63) unless there is intrinsic myocardial disease, including atrophy in chronic constriction or coronary involvement by scar tissue, or both. Balloon flotation catheters permit early physiologic diagnosis (Fig. 3). Constrictive physiology resembles that of restrictive cardiomyopathy except that in myopathy, diastolic filling is usually less rapid and the left ventricle usually remains less compliant than the right; as a result, left ventricular diastolic pressure is usually higher.

Latent (occult) constriction. Some patients with nonspecific symptoms and often a history of disease consistent with pericarditis have suggestive but nondiagnostic pressures. Intravenous fluid loads provoke the characteristic diastolic restriction curves (64).

Previously reported anecdotally (65), the intermediate syndrome, *effusive-constrictive pericarditis* in patients with simultaneous constriction and a layer of tamponading fluid, has been carefully analyzed (66). Because it is usually dominated by tamponade dynamics, fluid removal reveals clinical and hemodynamic constriction immediately or after further pericardial fibrosis.

Cardiography of Pericardial Disease

Electrocardiogram

Evolutionary ST-T changes. The traditional quasi-specific evolutionary ST-T changes of acute pericarditis (6) have been codified in four stages (any of which may not be recorded) (67,68); *stage I*, ST segment deviations; *stage II*, return of ST junctions to baseline and flattening of the T wave; *stage III*, T wave inversions; and *stage IV*, restitution to prepericarditis tracing. Variability of response was recognized including typical and atypical variants of this process. Typical *stage I* ST elevations in most leads that evolve to any other stage remain highly specific. The principal differential diagnosis of the stage I ''typical'' electrocardiogram of acute pericarditis is the apparently normal variant ''*early repolarization*'', frequent among neurotic and psy-

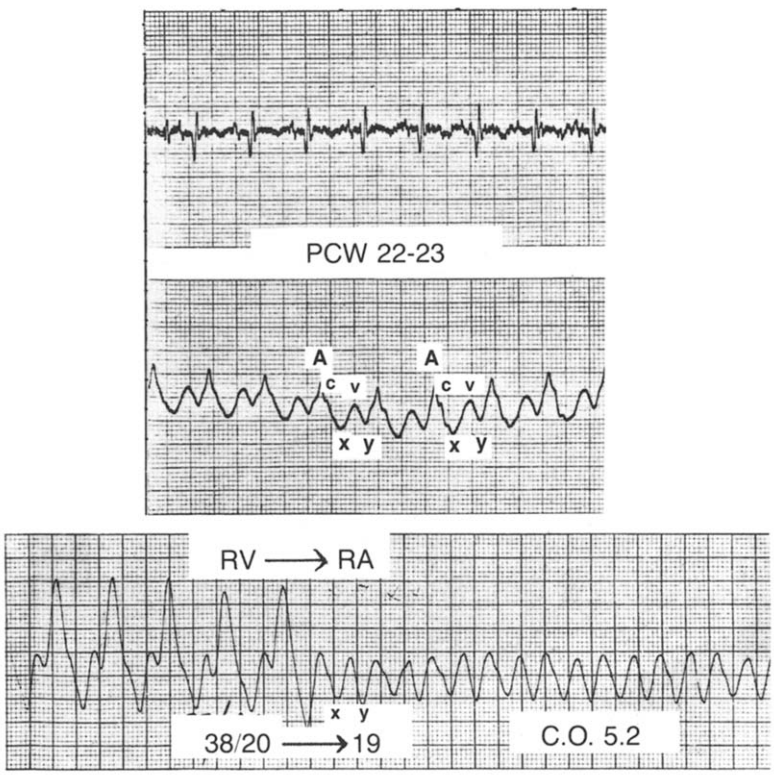

Figure 3. *Bedside diagnosis of constriction.* Unretouched pressure tracings from patient's chart showing (**top**), prominent *x* and *y* descents in pulmonary capillary wedge (PCW) tracing (pressure = 22–23 mm Hg). **Bottom**, pullthrough from right ventricle (RV) to right atrium (RA): high right ventricular diastolic pressure rebounding from ''dip'' to more than one-third of right ventricular systolic pressure; right atrial pressure with prominent *x* and *y* descents. C.O. = cardiac output.

chotic persons. The amplitude ratio, ST junction/T wave of 0.25 or less in lead V_6, was 100% specific for "early repolarization" (69). Although widespread PR segment deviations occur much more often with acute pericarditis and the ST vector is more likely to be to the left of the QRS vector, these are imperfect discriminators (70).

PR segment deviations. A "new" finding, previously overlooked because of the optical illusion of ST deviation when the natural TP baseline is ignored, is *PR segment deviation*—depression in most leads; elevation in aVR—a highly sensitive sign of unknown specificity (67,68). Among 50 patients with uncomplicated acute pericarditis and classic stage I ST segment deviations, 41 had PR segment deviations. The ST (J) vector was oriented left-anterior-inferior, consistent with the generalized subepicardial ventricular myocarditis of acute pericarditis; the PR vector was oriented right-posterior-superior—directly opposite to the P vector—representing the corresponding atrial myocarditis. Wide dispersion of the T vector in stage III was consistent with inhomogeneity of post-injury ventricular recovery. Ten nondiagnostic or less diagnostic electrocardiographic patterns were described, including three normal and "nonspecific" tracings, four variants of the typical sequence and three atypical variants simulating local myocardial injury (71,72). A subsequent investigation of the earliest electrocardiographic changes (that is, when diagnosis may be urgent) revealed that 43% had atypical or nonspecific tracings (73). Some patients with only PR segment deviations shortly developed typical stage I ST changes. Thus, a diagnostic electrocardiographic pattern developed soon after onset in about two-thirds of patients (72).

Electrical alternans. Although not the only etiology of serious pericardial effusions, metastatic malignancy is the principal cause of increasing identification of electrical alternans, mostly alternating QRS or QRS-T, though P-QRS-T ("total") alternation remains pathognomonic for tamponade (74). During pericardiocentesis, prompt disappearance of alternation with the first relatively small fluid decrement usually accompanies disproportionately great relief of symptoms and lessening signs of cardiac compression (74). This reverses the usual sequence that provoked circulatory embarassment—the last small increment precipitates acute tamponade (the "last straw" phenomenon). Although this suggested a hemodynamic factor in alternans, echocardiography shows that the common correlate is "swinging" of the heart with one excursion over each two cycles (75). Large cardiac pendular and rotary arcs have been shown experimentally (76), but to cause alternation the periodicity must synchronize with half the heart rate. Yet, more than one mechanism may be involved because not every swinging heart shows alternation, and irregular ("syncopated") 2:1 alternans with atrial ectopic beats has now been reported (77). Moreover, electrical alternation during tamponade by only 200 ml of fluid (total pericardial contents) in a patient with a very thick parietal pericardium suggests a causative role for pericardial stiffness (65).

Echocardiography

Pericardial effusion. Echocardiography has proved highly reliable for diagnosing pericardial effusion (Table 2) (75). Prospective studies of M-mode echocardiography delineated small, moderate and large effusions (78), although fine quantitation of effusion size has not been successful. But the sequence of accumulation provides a gross estimate: Fluid first appears as increased separation of epicardium and posterior pericardium during systole, progressing to separation during systole and diastole. Next, with moderate-sized effusions there is continuous separation of the epicardial and pericardial echoes, with the pericardial echo flat

Table 2. Echocardiogram in Pericardial Effusion and Cardiac Tamponade (NB: varying sensitivities and specificities)

I. Pericardial effusion
- A. Echo-free space-posterior to LV (small to moderate effusion)
  - -posterior and anterior (moderate to large effusion)
  - -behind left atrium (large to very large effusion)
- B. Decreased movement of posterior pericardium-lung interface
- C. RV pulsations brisk (with anterior fluid)
- D. Aortic root movement abnormal or attenuated
- E. "Swinging heart" (large effusions)
  - Periodicity 1:1 or 2:1
  - RV and LV walls move synchronously
  - Mitral/tricuspid pseudoprolapse
  - Alternating mitral E-F slope and aortic opening excursion

II. Cardiac tamponade: changes of effusion plus
- A. RV compression
  - RV diameters decreased
  - Early diastolic collapse of outflow tract
- B. Inspiratory effects (with pulsus paradoxus)
  - RV expands
  - IV septum shifts to left
  - LV compressed
  - Mitral D-E amplitude decreased
    - -E-F slope decreased or rounded
    - -open time* decreased
  - Aortic valve* opening decreased; premature closure
  - Echographic stroke volume decreased
- C. Notch in RV epicardium during isovolumic contraction
- D. Coarse oscillations of LV posterior wall

III. 2-D echocardiography: most of the above plus
- A. RA free wall indentation during late diastole or isovolumic contraction.
- B. LA free wall indentation (cases with fluid behind LA)
- C. SVC and IVC congestion (unless volume depletion)

*Often difficult to define during pericardial effusion; mitral valve may open only with atrial systole during inspiration. IV = interventricular; IVC = inferior vena cava; LA = left atrium; LV = left ventricle; RA = right atrium; RV = right ventricle; SVC = superior vena cava; 2D = two-dimensional.

or moving slightly. In the absence of adhesions, fluid also appears anteriorly in moderate to large effusions. The pericardial clasp of the left atrium (6) prevents most posterior fluid from penetrating behind it, but very large effusions often extend behind the mitral anulus and lower left atrium and into the pericardium's oblique sinus. Diagnostic problems arise from left pleural effusions, epicardial fat, tumor tissue, adhesions and enlargement of other cardiovascular structures. Exaggerated cardiac motion, particularly "swinging," often is associated with pseudoprolapse and false systolic anterior movement of the atrioventricular valves with large effusions.

Tamponade and pulsus parodoxus. Tamponade shows all these findings and also progressive compression of the right ventricle (44) with early diastolic collapse of its outflow tract (45). *Pulsus paradoxus* is associated with inspiratory leftward movement of the interventricular septum as the right ventricle expands at the expense of the left, often with premature mid-systolic closure of the aortic valve and delayed opening of the mitral valve (which may only be opened by atrial systole) during inspiration.

Two-dimensional echocardiography. This has improved diagnosis both because more structures are seen (and in a more dynamic way) and because findings responsible for false positive and negative M-mode diagnoses of effusion, including pericardial adhesions, are identified. Clotting of intrapericardial blood and subsequent organization to the point of adhesions and fibrosis has been observed as a progressive increase in the intensity of pericardial space echoes (79). *Serial echocardiography* has proved valuable in following the course of pericardial effusions and in detecting hemodynamic compromise.

Adhesive pericardial disease and constriction. In these conditions, the echocardiogram has been helpful but relatively nonspecific (80,81). Pericardial thickening is suggested by a condensed or doubled echo that may move with the left posterior wall echo, with or without an intervening (presumably fluid-filled) space. *Constriction* may reduce cavity size, but most consistently imposes flattening of posterior wall motion in mid- to late diastole, usually with no posterior "depression" after atrial systole; the post-P wave endocardial echo often moves less than 1 mm posteriorly. The atria are dilated. (These signs are not pathognomonic and can be seen with restrictive cardiomyopathy and acute cardiac dilation producing restriction by a normal pericardium.) The mitral E-F slope may be rapid, with early mitral closure. Though atrial systole makes little or no impression on the posterior wall, after the P wave it often produces brisk posterior and subsequent anterior motion of the interventricular septum; that is, the sudden increase in left ventricular volume displaces the septum because the posterior wall cannot "give." (This is not seen in restrictive cardiomyopathy and is distinguished from right ventricular volume overload in which anterior septal motion begins later, with ventricular systole.) During inspiration both interatrial and interventricular septa bulge to the left. At very high right ventricular diastolic pressure, the pulmonary valve opens prematurely, showing brisk diastolic posterior motion, implying right ventricular pressure transiently exceeding pulmonary artery pressure. After atrial systole there may be marked inspiratory deepening of the pulmonary valve A wave (82). In two-dimensional echocardiograms, the pericardium appears as an immobile single or double encasement of the ventricles that abruptly ends ventricular expansion; atrioventricular valves are hyperactive.

Roentgenography and Imaging

Because no size or shape of the cardiopericardial silhouette is specific for pericardial lesions, plain chest X-ray films are of little diagnostic value, except to identify calcifications at its periphery, epicardial fat lines within it—an occasional sign of effusion—and pericardial cysts. Positive contrast angiography may demonstrate wall thickening and some dynamic features; arteriography may show coronary vessels lying deep to an effusion or a cicatrix. Negative contrast (carbon dioxide) right atriography, once useful, is no longer needed. Computed tomography and allied techniques have been increasingly valuable in identifying constriction, fat pads, pericardial cysts, tumors and effusions, although for effusions, echocardiography usually suffices. Technetium pertechnetate, gallium-87 and other isotopes promise to demonstrate pericardial fluid and epicardial inflammation, but require further development.

Clinical Pericardial Disease

Pericardial friction. The rub, clinical hallmark of pericarditis, traditionally labeled a "to and fro" phenomenon, was finally characterized as usually audible and recordable as having three components (83). Prospective, multiple-auscultator studies with phonocardiography in 100 patients showed triphasic rubs in more than half of those with sinus rhythm (84). Some biphasic ("to and fro") rubs were accounted for by absence of atrial systole, others by summation between diastolic and atrial (presystolic) rub components. Thus, most rubs are characteristically or potentially triphasic. Fifteen patients had a monophasic rub, with one confined to atrial systole. In a patient with complete atrioventricular block an atrial diastolic component produced a quadriphasic rub (85), raising the question of the true mechanism of pericardial rubs; that is, atrial diastole must be a feeble movement, and because rubs are common with effusion and tamponade (84), are they really friction (rubbing) sounds?

Acute pericarditis and arrhythmias. It had been thought that pericarditis must engulf the sinus node, lying a millimeter within the right atrial wall; this was traditionally thought

to cause arrhythmia in acute pericarditis. A prospective study of 100 patients with acute pericarditis showed that arrhythmias were present only in a few of those with significant heart disease (86). A retrospective study in a different patient population confirmed this (73). Finally, elegant anatomic studies (87) demonstrated that the sinus node is virtually immune to involvement by surrounding acute pericarditis and that arrhythmias occurred only in patients who had disease of the myocardium or valves.

"New" forms of constriction. Traditionally termed "chronic," constrictive pericarditis became uncommon in Western countries by the 1950s, and acute and subacute constrictive pericarditis were described (5). Uremic constriction recently appeared in patients permitted long survival by dialysis (88). Increased (though relatively small) numbers of cases of postoperative constriction have followed the increase in cardiac surgery including coronary bypass procedures (89). Intense mediastinal radiation therapy has added to the cases of constriction.

Surgery of the pericardium. Surgical indications in pericardial disease have been unchanged except for earlier, therefore easier, pericardiectomy in acute and subacute constriction (89). Resection of pericardial "windows" has become popular for biopsy, palliation of neoplastic effusions and relief of resistant or relapsing acute pericarditis and effusions, although resistant effusions are best treated by extensive pericardiectomy. Formal studies are not available, but clinical experience indicates that pericardial windows tend to close, often with recurrence of effusion. Resection or pericardiectomy for resistant inflammatory lesions is a desperate measure with widely varying results; many cases continue producing symptoms. A noteworthy advance in managing tamponade is subxiphoid resection and exploration.

Right ventricular infarction. Contrary to previous impressions, a functioning right ventricle is important to maintain cardiac output, because right ventricular infarction often produces a low output state. The pericardium has a definite role: pericardiotomy after experimental right ventricular infarction improves left ventricular filling and output (90). Moreover, right ventricular infarction shows restrictive hemodynamics, owing to the presence of the pericardium, with reduced left ventricular preload due to impaired right ventricular systolic function and increased pericardial pressure.

Clinical investigation of cardiac tamponade. A landmark study (91) of 56 patients with cardiac tamponade quantitated the occurrence of clinical findings. Blood pressure was often well maintained with systolic pressure 100 mm Hg or more in 36 patients. Pulse pressure averaged 49 mm Hg (40 mm Hg or more in 27). Pulsus paradoxus of 20 mm Hg or more, present in 41 patients, involved the whole pulse pressure in 12. Right ventricular dimensions increased and left ventricular dimensions decreased during inspiration, except in one patient who had left ventricular dysfunction. Fifty-two patients had an enlarged cardiac silhouette. Sixteen patients with tamponade had a pericardial rub (consistent with previous observations that the rub is common despite pericardial effusion, including tamponade)(84). Heart sounds were diminished in only 19 patients. Tachycardia (heart rate 100 beats/min or more) was present in 43 patients.

Immunopathic pericarditis. A long-standing question is how often pericarditis may be an immune or idiosyncratic reaction, triggered, for example, by injuries and in response to medications, and if such triggers provoke latent or smoldering infection, particularly by viruses. An important therapeutic challenge has been *recurrent acute pericarditis* in the absence of overt pericardial infection. In many cases recurrence is only suppressed with continuous or repetitive anti-inflammatory treatment; some patients become "hooked"—difficult or impossible to wean from corticosteroid agents (92).

A clinical model of immunopathic pericarditis is the postpericardiotomy syndrome, that is, acute postoperative but "nonsurgical" pericarditis, often with effusion and pleural involvement occurring in 15 to 20% of adult patients. The elegant studies of Engle et al. (93) showed an incidence of postpericardiotomy syndrome proportional to the extent of surgical trauma in 36% of children over 2 years old. Antiheart antibody appeared in some patients whose diagnostic high titers correlated with the clinical syndrome. In 70% of patients with postpericardiotomy syndrome, a significant rise in titer to one or more viruses was a nonspecific response to agents prevalent in the community. The working hypothesis of Engle et al. was that postpericardiotomy syndrome is an immunologically determined response of the epicardial myocardium, probably triggered by latent or fresh viral illness; appearance of antiheart antibody is related to the patient's age and previous immunologic experience.

The *postmyocardial infarction syndrome*, perhaps related to the postpericardiotomy syndrome, occurs in very few patients. It is difficult to distinguish from infarct (epistenocardiac) pericarditis and the role of antiheart antibody has been uncertain. (*Antipericardial* antibodies are unknown.)

Etiologic Forms of Pericardial Disease

Qualitative and quantitative changes in the vast etiologic spectrum of pericarditis have followed changing prevalence, effective treatment of infections, and conditions giving rise to new forms of pericarditis (for example, dialysis has solved most uremic pericarditis, but permits both "dialysis pericarditis" and uremic constriction).

Infective pericarditis. A recent review (94) summarized the status of infective pericarditis. In Western countries *purulent pericarditis* is less frequent than in pre-antibiotic days, occurring more often in children and in debilitated and immunocompromised patients. The bacterial spectrum includes an apparent decline in staphyococcal, streptococcal and pneumococcal infections although epidemiologically

sound studies are lacking. Pus still should be evacuated promptly and quantitatively, usually by surgery, because pyogenic infections tend to cause tamponade and constriction. Fortunately, the level reached by antibiotics in pericardial fluid is excellent and the serum level can be used to judge the pericardial level (95). *Tuberculous pericarditis* has decreased in incidence, and is no longer the prime cause of constriction, although it is a popular "rule out." *Viral pericarditis* probably accounts for most community-acquired infections (96), although viral cultures usually fail; fourfold or greater increases in convalescent serum titer are usual but, because of the benignity of most infections, are not tested. The most common viruses are the Coxsackie group, echoviruses and, probably, adenovirus. Individual cases of rickettsial, mycotic, parasitic and many hitherto "uncommon" organisms like *Legionella pneumophilia* continue to be reported. In post-surgical, debilitated and immunocompromised hosts, *gram-negative bacilli* are relatively common. Among children, *Haemophilus influenzae* pericarditis still has an ominous prognosis for exceptionally rapid tamponade and constriction. The influence of antibiotics on purulent pericarditis was summarized (94): 1) incidence has decreased; 2) survival has increased; 3) drainage is still necessary; 4) some cases are masked; 5) resistant and unusual organisms have appeared; 6) there are more hospital-acquired cases; and 7) there is a greater post-surgical incidence (especially cardiac surgery).

Wounds. Chest, heart and pericardial wounds produce major emergencies, particularly tamponade that is not always readily recognized. Many signs may be lacking because of rapid pericardial hemorrhage with blood volume depletion. Experience favors early surgical exploration and drainage (97).

Uremic pericarditis. This condition usually appears shortly before or after beginning dialysis, which has made it newly important (88,98), because previous treatment was ineffective and pericarditis was a harbinger of death (6). The etiology is unknown because intrapericardial creatinine and related substances do not cause pericarditis. Yet the vast majority have a blood urea nitrogen (BUN) level of 60 mg/100 ml or more. Volume depletion, for example, during dialysis, may precipitate latent tamponade. *Uremic constriction* has become a result of long survival (99). With time and satisfactory dialysis, some patients now develop *dialysis pericarditis*, which can occur at normal BUN levels. Some patients have intercurrent infection, traditionally pneumoccal, but now presumably mostly viral. (Hepatitis virus, common in dialysis units, is associated with pericarditis.) Infected uremic patients may be those with typical stage I electrocardiographic changes, such ST-T changes being rare in uremia because even severe uremic pericarditis usually spares the myocardium. In uncomplicated cases, treatment is intense dialysis. Management of tamponade in uremic or dialysis pericarditis is by pericardiocentesis with prolonged catheter or surgical drainage, or pericardiectomy (88, 98). Medical treatment with intrapericardial or systemic anti-inflammatory agents is controversial because of the lack of a randomized controlled trial.

Radiation pericarditis. Although pericarditic effects of therapeutic radiation had been described (5,6), widespread use of mediastinal radiation for malignancy (particularly lymphomas and Hodgkin's disease) greatly multiplied the cases. A mediastinal dose of 4,000 rads or greater will produce acute fibrinous pericarditis and damage capillary and lymphatic endothelium, obstructing these vessels to produce effusion and tamponade; some patients develop local or generalized constriction (100).

Idiopathic pericarditis. The well known syndrome of idiopathic (formerly "acute benign") pericarditis occurring mostly in men, appears usually to be of viral origin. Some specific diseases, for example, lupus erythematosus, may first appear as an idiopathic pericarditis, so that women with "idiopathic" pericarditis should be appropriately tested.

Iatrogenic pericarditis. A host of physicians' treatments and maneuvers in addition to radiation and dialysis pericarditis, can affect the pericardium; this is seen most frequently in response to a variety of medications, notably procainamide and hydralazine (and sometimes in connection with drug-induced lupus) which leads to acute pericarditis and, rarely, to constriction. The great increase in cardiac surgery has produced much more of both the usual surgical pericarditis and delayed post-surgical (immunopathic?) pericarditis as well as immediate and delayed postoperative cardiac tamponade and constriction. During surgery, the delicate mesothelium probably is always lost or widely disrupted and, in appropriate patients, an immediate, delayed or recurrent pericardial syndrome develops.

References

1. Spodick DH. Medical history of the pericardium. Am J Cardiol 1970;26:447–54.
2. Shabetai R. The Pericardium. New York: Grune & Stratton, 1981:93,420.
3. Reddy PS, Leon DF, Shaver JA. Pericardial Disease. New York: Raven Press, 1982:369.
4. Spodick DH, ed. Pericardial Diseases. Philadelphia: FA Davis, 1976:4,312.
5. Spodick DH. Acute Pericarditis. New York: Grune & Stratton, 1959:133,153,181,182.
6. Spodick DH. Chronic and Constrictive Pericarditis. New York: Grune & Stratton, 1964:5,17,67,84,140,369.
7. Shabetai R, Fowler NO, Guntheroth WG. The hemodynamics of cardiac tamponade and constrictive pericarditis. Am J Cardiol 1970;26:480–9.
8. Shabetai R, Fowler NO, Gueron M. The effects of respiration on aortic pressure and flow. Am Heart J 1963;65:525–33.
9. Shabetai R, Fowler NO, Fenton JC. Restrictive cardiac disease: pericarditis and the myocardiopathies. Am Heart J 1965;69:271–80.
10. Shabetai R. The pathophysiology of cardiac tamponade and constriction. In Ref 4:67–90.

11. Shabetai R. The pericardium: an essay on some recent developments. Am J Cardiol 1978;42:1036–43.
12. Shabetai R, Fowler NO, Braunstein JR, Gueron M. Transmural ventricular pressures and pulsus paradoxus in experimental cardiac tamponade. Dis Chest 1961;39:557–68.
13. Shabetai R, Fowler NO, Fenton JC, Masangkay M. Pulsus paradoxus. J Clin Invest 1965;44:1882–98.
14. Shabetai R, Mangiardi L, Bhargava V, Ross J Jr, Higgins CB. The pericardium and cardiac function. Prog Cardiovasc Dis 1979;22:107–34.
15. Shabetai R, Grossman W. Profiles in constrictive pericarditis, restrictive cardiomyopathy and cardiac tamponade. In: Grossman W, ed. Cardiac Catheterization and Angiography. Philadelphia: Lea & Febiger, 1980:304–13.
16. Fowler NO, Shabetai R, Braunstein JR. Transmural ventricular pressures in experimental cardiac tamponade. Circ Res 1959;7:733–9.
17. Fowler NO. Physiology of cardiac tamponade and pulsus paradoxus II. Mod Concepts Cardiovasc Dis 1978;47:115–9.
18. Fowler NO, Engel PJ, Settle HP, Shabetai R. The paradox of the paradoxical pulse. Trans Am Clin Climatol Assoc 1978;90:27–8.
19. Fowler NO, Gabel M, Holmes JC. Hemodynamic effects of nitroprusside and hydralazine in experimental cardiac tamponade. Circulation 1978;57:563–7.
20. Guntheroth WG, Morgan BC, Mullins GL. Effect of respiration on venous return and stroke volume in cardiac tamponade. Circ Res 1967;20:381–90.
21. Morgan BC, Guntheroth WG, Dillard DH. Relationship of pericardial to pleural pressure during quiet respiration and cardiac tamponade. Circ Res 1965;16:493–8.
22. Reddy PS, Curtiss EI, O'Toole JD, Shaver JA. Cardiac tamponade: hemodynamic observations in man. Circulation 1978;58:265–72.
23. Friedman HS, Lajam F, Zaman Q, et al. Effect of autonomic blockade on the hemodynamic findings in acute cardiac tamponade. Am J Physiol 1977;232:H5–11.
24. Friedman HS, Lajam J, Calderon J, Zaman Q, Marino ND, Gomes JA. Electrocardiographic features of experimental cardiac tamponade in closed-chest dogs. Eur J Cardiol 1977;6:311–22.
25. Friedman HS, Sakurai H, Choe SS, Lajam F, Celis A. Pulsus paradoxus: a manifestation of marked reduction of left ventricular end-diastolic volume in cardiac tamponade. J Thorac Surg 1980;79:74–82.
26. Janicki JS, Weber KT. The pericardium and ventricular interaction, distensibility, and function. Am J Physiol 1980;238:H494–503.
27. Rabkin SW, Hsu PH. Mathematical and mechanical modeling of stress-strain relationship of pericardium. Am J Physiol 1975;229:896–900.
28. Holt JP. Ventricular end-diastolic volume and transmural pressure. Cardiology 1967;50:281–90.
29. Spotnitz HM, Kaiser GA. The effect of the pericardium on pressure-volume relations in the canine left ventricle. J Surg Res 1971;11:375–80.
30. Banchero N, Rutishauser WJ, Tsakiris AG, Wood EH. Pericardial pressure during transverse acceleration in dogs without thoracotomy. Circ Res 1967;20:65–77.
31. Bartle SH, Hermann JH. Acute mitral regurgitation in man. Hemodynamic evidence and observations indicating an early role for the pericardium. Circulation 1967;36:839–51.
32. Bemis CE, Serur JR, Borkenhagen D, Sonnenblick EH, Urschel CW. Influence of right ventricular filling pressure on left ventricular pressure and dimension. Circ Res 1974;34:498–504.
33. Buda AJ, Pinsky MR, Ingels NB, Daughters GT, Stinson EB, Alderman EL. Effect of intrathoracic pressure on left ventricular performance. N Engl J Med 1979;301:480–2.
34. Craig RJ, Whalen RE, Behar VS, McIntosh HD. Pressure and volume changes of the left ventricle in acute pericardial tamponade. Am J Cardiol 1968;22:65–74.
35. Ditchey R, Engler R, LeWinter M, et al. The role of the right heart in acute cardiac tamponade in dogs. Circ Res 1981;48:701–10.
36. Elzinga G, Piene H, DeJong JP. Left and right ventricular pump function and consequences of having two pumps in one heart. Circ Res 1980;46:564–74.
37. Glantz SA, Misbach GA, Moores WY, et al. The pericardium substantially affects the left ventricular diastolic pressure-volume relationship in the dog. Circ Res 1978;42:433–41.
38. LeWinter MM, Pavelec RS. Influence of the pericardium on left ventricular end-diastolic pressure segment relations during early and later stages of experimental chronic volume overload in dogs. Circ Res 1982;50:501–9.
39. Ferrans VJ, Ishihara T, Roberts WC. Anatomy of the pericardium. In Ref 3:15–29.
40. Roberts WC, Spray TL. Pericardial heart disease: a study of its causes, consequences and morphologic features. In Ref 4:11–66.
41. Miller AJ, Pick R, Johnson PJ. The production of acute pericardial effusion. The effects of various degrees of interference with venous blood and lymph drainage from the heart muscle in the dog. Am J Cardiol 1971;28:463–6.
42. Mangano DT. The effect of the pericardium on ventricular systolic function in man. Circulation 1980;61:352–7.
43. Spodick DH. Pathophysiology of disorders of the pericardium. In: HJ Levine, ed. Clinical Cardiovascular Physiology. New York: Grune & Stratton, 1976:621–34.
44. Schiller NB, Botvinick EH. Right ventricular compression as a sign of cardiac tamponade. Circulation 1977;56:774–9.
45. Armstrong WF, Schilt BF, Helper DJ, Dillon JC, Feigenbaum H. Diastolic collapse of the right ventricle with cardiac tamponade. Circulation 1982;65:1491–6.
46. Shiina A, Yaginuma T, Kando K, Kawai H, Hosada S. Echocardiographic evaluation of impending cardiac tamponade. J Cardiog 1979;9:555–63.
47. DeCristofaro D, Liu CK. The haemodynamics of cardiac tamponade and blood volume overload in dogs. Cardiovasc Res 1969;3:292–8.
48. O'Rourke RA, Fischer DP, Escobar EE, Bishop VS, Rapaport E. Effect of acute pericardial tamponade on coronary blood flow. Am J Physiol 1967;212:549–52.
49. Jarmakani JMM, McHale PA, Greenfield JC. The effect of cardiac tamponade on coronary haemodynamics in the awake dog. Cardiovasc Res 1975;9:112–7.
50. Wechsler AS, Auerback BJ, Graham TC, Sabiston DC. Distribution of intramyocardial blood flow during pericardial tamponade. J Thorac Cardiovasc Surg 1974;68:847–56.
51. Spodick DH. Acute cardiac tamponade: pathologic physiology, diagnosis and management. Prog Cardiovasc Dis 1967;10:64–96.
52. Ruskin J, Bache RJ, Rembert JC, Greenfield JC. Pressure-flow studies in man: effect of respiration on left ventricular stroke volume. Circulation 1973;48:79–85.
53. Spodick DH, Paladino DM. Exaggerated respiratory variation in left ventricular ejection time during lax pericardial effusion. Cardiology (in press).
54. Antman EM, Cargill V, Grossman W. Low-pressure cardiac tamponade. Ann Intern Med 1979;91:403–6.
55. Spodick DH. Acute cardiac tamponade. In: Chung EK, ed. Cardiac Emergency Care. 2nd ed. Philadelphia: Lea & Febiger, 1980:295–305.
56. Arom KV, Richardson JD, Webb G, Grover FL, Trinkle JK. Subxiphoid pericardial window in patients with suspected traumatic pericardial tamponade. Ann Thorac Surg 1977;23:545–9.

57. Prager RL, Wilson CH, Bender HW. The subxiphoid approach to pericardial disease. Ann Thorac Surg 1982;34:6–9.

58. Martins JB, Manuel W, Marcus ML, Kerber RE. Comparative effect of catecholamines in cardiac tamponade: experimental and clinical studies. Am J Cardiol 1980;46:59–66.

59. Kerber RE, Jascho JA, Litchfield R, Wolfson P, Ott D, Pandian NJ. Hemodynamic effects of volume expansion and nitroprusside compared with the pericardiocenesis in patients with acute cardiac tamponade. N Engl J Med 1982;307:929–31.

60. Reddy PS, Curtiss EI, O'Toole JD, Shaver JA. Cardiac tamponade: hemodynamic observations in man. Circulation 1978;58:265–72.

61. Van de Werf F. The Genesis of the Third Heart Sound. Leuven: Faculty of Medicine, 1982:116–20.

62. Spodick DH. Acoustic phenomena in pericardial disease. Am Heart J 1971;81:114–24.

63. Armstrong TG, Lewis BS, Gotsman MS. Systolic time intervals in constrictive pericarditis and severe primary myocardial disease. Am Heart J 1973;85:6–12.

64. Bush CA, Stang JM, Wooley CF, Kilman JW. Occult constrictive pericardial disease. Circulation 1977;56:924–30.

65. Spodick DH, Kumar S. Subacute constrictive pericarditis with cardiac tamponade. Chest 1968;54:62–6.

66. Hancock EW. Subacute effusive constrictive pericarditis. Circulation 1971;43:183–92.

67. Spodick DH. Diagnostic electrocardiographic sequences in acute pericarditis. Significance of P-R segment and P-R vector changes. Circulation 1973;48:575–80.

68. Spodick DH. Electrocardiogram in acute pericarditis. Distributions of morphologic and axial changes by stages. Am J Cardiol 1974;33:470–2.

69. Ginzton LE, Laks MM. The differential diagnosis of acute pericarditis from the normal variant: new electrocardiographic criteria. Circulation 1982;65:1004–9.

70. Spodick DH. Differential characteristics of the electrocardiogram in early repolarization and acute pericarditis. N Engl J Med 1976;295:523–6.

71. Spodick DH. Differential diagnosis of acute pericarditis. Prog Cardiovasc Dis 1971;14:192–209.

72. Spodick DH. Pathogenesis and clinical correlation of electrocardiographic abnormalities of pericardial disease. In: Rios G, ed. Clinico-Electrocardiographic Correlations. Philadelphia: FA Davis, 1977:201–14.

73. Bruce ME, Spodick DH. Atypical electrocardiogram in acute pericarditis: characteristics and prevalence. J Electrocardiol 1980;13:61–6.

74. Spodick DH. Electric alternation of the heart. Its relation to the kinetics and physiology of the heart during cardiac tamponade. Am J Cardiol 1962;10:155–65.

75. Shah PM, Nanda NC. Echocardiography in the diagnosis of pericardial effusion. In Ref 4: 125–30.

76. Brody D, Copeland GD, Cox JW, et al. Experimental and clinical aspects of total electrocardiographic alternation. Am J Cardiol 1973;31:254–9.

77. Doi YL, Sugiura T, Bishop RL, Spodick DH. Syncopated electrical alternans. Am Heart J 1981;101:243–6.

78. Horowitz MS, Schultz CS, Stinson EB, Harrison DC, Popp RL. Sensitivity and specificity of echocardiographic diagnosis or pericardial effusion. Circulation 1974;50:239–47.

79. Allen JW, Harrison EC, Camp JC, Borsari A, Turnier E, Lau FYK. The role of serial echocardiography in the evaluation and differential diagnosis of pericardial disease. Am Heart J 1977;93:560–7.

80. Schnittger I, Bowden RE, Abrams J, Popp RL. Echocardiography: pericardial thickening and constrictive pericarditis. Am J Cardiol 1978;42:388–95.

81. Voelkel AG, Pietro DA, Folland ED, Fisher ML, Parisi AF. Echocardiographic features of constrictive pericarditis. Circulation 1978;58:871–5.

82. Doi YL, Sugiura T, Spodick DH. Motion of pulmonic valve and constrictive pericarditis. Chest 1981;80:513–5.

83. Spodick DH. Pericardial friction. Characteristics of pericardial rubs in fifty consecutive prospectively studied patients. N Engl J Med 1968;278:1204–7.

84. Spodick DH. The pericardial rub: a prospective, multiple observer investigation of pericardial friction in 100 patients. Am J Cardiol 1975;35:357–62

85. Spodick DH, Marriott HJL. Atrial diastolic friction. Chest 1975;68:122–3.

86. Spodick DH. Arrhythmias during acute pericarditis: a prospective study of one hundred consecutive cases. JAMA 1976;235:39–41.

87. Lekieffre J, Medvedowsky JL, Thery C. Le noeud sinusal normal et pathologique. Rueil-Malmaison: Editions Sandoz, 1979:162.

88. Comty CM, Wathen RL, Shapiro FL. Uremic pericarditis. In Ref 4:219–36.

89. Miller JI, Mansour KA, Hatcher CR. Pericardiectomy. Current indications, concepts and results in a university center. Ann Thorac Surg 1982;34:40–5.

90. Goldstein JA, Vlahakes GJ, Verrier ED, et al. The role of right ventricular systolic dysfunction and elevated intrapericardial pressure in the genesis of low output in experimental right ventricular infarction. Circulation 1982;65:513–22.

91. Guberman B, Fowler NO, Engel PJ, Gueron M, Allen JM. Cardiac tamponade in medical patients. Circulation 1981;64:633–40.

92. Spodick DH. Acute pericardial disease: pericarditis, effusion and tamponade. JCE Cardiology 1979;14:9–27.

93. Engle MA, Klein AA, Hepner S, Ehlers KH. The postpericardiotomy and similar syndromes. In Ref 4:211–8.

94. Spodick DH. Infective pericarditis: etiologic and clinical spectra. In Ref 3:307–12.

95. Tan JS, Holmes JC, Fowler NO, Manitsas GT, Phair JP. Antibiotic levels in pericardial fluid. J Clin Invest 1974;53:7–12.

96. Burch GE: Acute viral pericarditis. In Ref 4:149–58.

97. Harken DE: Surgery of the pericardium. In Ref 4:287–90.

98. Buselmeier TJ, Simmons RL, Najarian JS, Mauer SM, Matas AJ, Kjellstrand CM. Uremic pericardial effusion. Treatment by catheter drainage and local nonabsorbable steroid administration. Nephron 1976;16:371–80.

99. Lindsay J, Crawley IS, Callaway GM. Chronic constrictive pericarditis following uremic hemopericardium. Am Heart J 1970;79:390–5.

100. Stewart JR, Fajardo LF. Radiation-induced heart disease: clinical and experimental aspects. Radiol Clin North Am 1971;9:511–31.